Remarks

Claims 1 through 26 are pending. Claims 11-13 and 24-26 are canceled. Claims 1, 9, 10 14, 22 and 23 are amended. Claims 1-10 and 14-23 remain under consideration.

Amendments to claims 1, 9, 10, 14, 22, and 23 were made to correct typographical errors. No new matter is introduced by these amendments.

§ 112 Rejections

Claims 14 through 26 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Claims 24-26 have been canceled. Of the remaining claims, only claim 14 is independent. Applicant respectfully traverses the rejection.

Claim 14 recites a method of preventing dermonecrosis caused by venom-induced immune dysregulation, the method comprising applying a therapeutically effective amount of an immune response modifier compound to the site of the venom induced-immune dysregulation.

The rejection appears to be two-fold. First, the Office Action states that the "breadth of the claim is broad since it encompasses envenomation result (sic) from any and every organisms (sic) in the world." This characterization of the scope of claim 14 is inaccurate. Claims 14 is limited to preventing *dermonecrosis caused by venom-induced immune dysregulation*, i.e., claim 14 is limited to preventing a particular condition - dermonecrosis - that can result, in some circumstances, from immune dysregulation resulting from a bite from a *venomous animal.* Applicant has provided examples of prevention of dermonecrosis resulting from venomous bites of *Loxoscelec reculsa* and have identified additional species, the *venomous* bites or stings of which are known to cause dermal lesions that can progress to *dermonecrosis* (page 5, lines 18-26) resulting from venom-induced immune dysregulation. Therefore, claim 14 does not purport to cover prevention of envenomation by any species of organism. Nor does claim 14 purport to cover prevention of all types of lesions that result from envenomation, for example, lesions resulting from an allergic reaction to the venom. Rather, claim 14 covers preventing dermonecrosis caused by venom-induced dysregulation. Applicant submits that the scope of claim 14 is commensurate with the scope of Applicant's disclosure.

Second, the Office Action argues that a claim to preventing a medical condition is highly unlikely and unpredictable. Furthermore, the Office Action states, it is unclear as to the degree of prevention offered by the method of claim 14, because the specification does not disclose the extent of prevention achieved. Applicant respectfully disagrees with the positions set forth in the Office Action. "Prevent" is defined as meaning "to keep from happening" or "to impede." American Heritage® Dictionary of the English Language, third edition, Houghton Mifflin Company (1996). "Impede" is defined as meaning "to retard or obstruct the progress of." Nothing in the meaning of "prevent" explicitly or inherently communicates a particular degree of prevention. Applicant has used the term "preventing" to mean any degree of impeding - retarding or obstructing - the progression of dermonecrosis by treatment with a therapeutically effective amount of an immune response modifier compound. This position is supported by the use of the phrase "therapeutically effective amount" to describe the amount of immune response modifier compound that is applied using the method. The definition of "therapeutically effective amount" provided in Applicant's disclosure from page 4, line 27 through page 5, line 2 explicitly recites amelioration of symptoms or preventing dermonecrosis. These are not provided as separate standards, but as alternative, synonymous standards, each directed toward a particular method of Applicant's invention.

The Office Action states that absolute prevention of a medical condition is highly unlikely and highly unpredictable. Even if, for the sake of argument, the position stated in the Office Action is true, the position is irrelevant to the present application because claim 14 does not and did not claim "absolute prevention" of dermonecrosis. Applicant's use of the term "preventing" is explained above and contemplates any degree of prevention.

Applicant submits that claim 14 conforms to the requirements of 35 U.S.C. § 112, first paragraph. Each of claims 15-22 depends, directly or indirectly, from claim 14. Therefore, claims 15-22 also conform to the requirements of 35 U.S.C. § 112, first paragraph, for at least all of the reasons set forth above regarding claim 14.

In summary, Applicant submits that claims 14-22 conform to the requirements of 35 U.S.C. § 112, first paragraph. Withdrawal of the rejection with respect to claims 14-22 is respectfully requested.

§ 103 Rejections

Claims 1-26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 98/17279 (Tomai) and U.S. Pat. No. 6,110,929 (Gerster) in view of Bitterman-Deutsch *et al.*, Merigian and Blaho; Mosbech *et al.*, Binder, and Auerbach *et al.* Claims 11-13 and 24-26 have been canceled. Of the remaining claims, only claims 1 and 14 are independent. Claim 1 recites a method of treating dermal lesions caused by venom-induced immune dysregulation, the method comprising applying a therapeutically effective amount of an immune response modifier compound to the site of the lesion. Claim 14 recites a method of preventing dermonecrosis caused by venom-induced immune dysregulation, the method comprising applying a therapeutically effective amount of an immune response modifier compound to the site of venom-induced dysregulation.

Tomai teaches imidazoquinoline amine compounds. Gerster teaches thizoloquinoline compounds. The Office Action acknowledges that neither Tomai nor Gerster teaches that the imidazoquinoline amine compounds or the thiazoloquinoline compounds are useful for treating or preventing dermal lesions caused by venom-induced immune dysregulation.

The Office Action cites Bitterman-Deutsch *et al.*, Merigian and Blaho; Mosbech *et al.*, Binder, and Auerbach *et al.* as secondary references and suggests that it would have been obvious for one of ordinary skill in the art to combine any one of these references with either Tomai or Gerster to arrive at the present invention.

The rejections of claims 1-26 under 35 U.S.C. § 103(a) fail to set forth a *prima facie* case of obviousness. M.P.E.P. § 706.02(j) states that a rejection under 35 U.S.C. § 103 should set forth in the Office Action:

(1) the relevant teachings of the prior art relied upon;

(2) the difference or differences in the claim over the applied references;

(3) the proposed modification of the applied references necessary to arrive at the claimed subject matter; and

(4) an explanation of why such a proposed modification would have been obvious to one of ordinary skill in the art at the time the invention was made.

Further, M.P.E.P. § 706.02(j) states that in order to establish a *prima facie* case of obviousness, three basic criteria must be met:

(1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;

(2) there must be a reasonable expectation of success;

(3) the prior art references must teach or suggest all of the claim limitations. Moreover, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure.

With regard to the present invention, it is unclear, for example, why one of ordinary skill in the art would have been motivated to combine either Tomai or Gerster with either Mosbech *et* al. or Auerbach *et* al. Tomai and Gerster teach that the compounds described in those references are useful for treating T_H2-mediated (e.g., IgE-mediated) conditions. The Office Action cites Mosbech *et al.* as teaching that bee stings or wasp stings can result in allergic reactions. The Office action also cites Auerbach *et al.* as teaching that jellyfish envenomation can cause allergic dermatitis. The conditions discussed in each of Mosbech *et al.* and Auerbach *et al.* are T_H2-mediated allergic conditions. Conversely, the present invention relates to treating conditions - lesions and dermonecrosis - that result from T_H2-*independent* venom-induced immune dysregulation. For example, venom-induced dermonecrosis is independent of serum or tissue factors (Wasserman and Anderson, *J. Toxicol. Clin. Toxicol.*, 21(4&5):451-472, (1983-1984), see, for example, page 455-456).

The Office Action states that employing the imidazoquinoline and thiazoloquinoline compounds to treat or prevent dermal lesions caused by jellyfish and bee envenomation would be reasonably expected to be effective regardless of the underlying mechanism of action of how the dermal lesions developed. It is argued that the imidazoquinoline and thiazoloquinoline compounds are known to be useful in blocking IgE and eosinophil activities, which are said to be important for allergic dermatitis. Applicant does not claim treatment of allergic dermatitis or lesions arising from allergic reactions. Applicant claims treating lesions or preventing dermonecrosis resulting from venom-induced immune dysregulation. Allergic conditions (e.g., allergic dermatitis) and venom-induced immune dysregulation are distinct, unrelated conditions and the lesions arising from each condition have different causes and are, therefore, responsive to different modes of treatment. Contrary to the position stated in the Office Action, the different

underlying mechanisms responsible for T_H2-mediated (e.g., allergic dermatitis) lesions and T_H2-independent lesions (e.g., those resulting from venom-induced immune dysregulation) are important because the underlying mechanism that causes a particular lesion to develop helps define potentially effective treatment strategies. Consequently, it does not follow that a treatment for allergic conditions would also be useful for treating lesions or preventing dermonecrosis resulting from venom-induce immune dysregulation.

Because Applicant claims treatment of lesions other than those described in the secondary references, there must be some etiological connection between the types of lesions described in the secondary references and the lesions treatable using Applicant's invention in order to provide one skilled in the art with the motivation to combine the references as suggested in the Office Action, and thereby set forth a *prima facie* case of obviousness. No such connection between T_H2-mediated lesions - e.g., allergic dermatitis lesions - and T_H2-independent dermonecrosis or lesions resulting from venom-induce immune dysregulation exists and, consequently, no such connection has been set forth in the Office Action. The Office Action fails to provide reasoning why one of skill in the art would have been motivated to combine Tomai or Gerster with either Mosbech *et al.* or Auerbach *et al.* to treat a T_H2-independent condition.

The combination of either Tomai or Gerster with either Mosbech *et al.* or Auerbach *et al.* also fails to provide a reasonable expectation of success treating lesions or preventing dermonecrosis resulting from venom-induce immune dysregulation with a compound useful for treating T_H2-mediated allergic conditions. There must be some connection or commonality between the conditions treatable by the prior art treatments and the conditions treatable using Applicant's method in order to provide one skilled in the art with a reasonable expectation that the known treatments could also successfully treat the T_H2-independent conditions treatable by Applicant's methods. As discussed in detail above, no such connection between the T_H2-mediated conditions in the prior art and the T_H2-independent conditions treatable by the present invention has been established in the Office Action.

Consequently, Applicant submits that the rejection of the claims 1-10 and 14-22 under U.S.C. § 103(a) based on the combination of either Tomai or Gerster with either Mosbech *et al.* or Auerbach *et al.* is improper and should be withdrawn.

It is also unclear why, for example, why one of ordinary skill in the art would have been motivated to combine either Tomai or Gerster with either Bitterman-Deutsch *et al.*, Merigian and

Blaho, or Binder. The Office Action cites Bitterman-Deutsch *et al.* as teaching that necrotic cutaneous ulcerations caused by venomous *Loxosceles reclusus* bites may be treated with dapsone because dapsone presumably reduces activity of polymorphonuclear (PMN) leukocytes. The Office Action cites Merigian and Blaho as teaching that *L. reclusus* envenomation leads to accumulation of PMN leukocytes and that the local bite area is often filled with inflammatory infiltration of neutrophils and eosinophils. Finally, the Office Action cites Binder as teaching that *L. reclusus* envenomations can cause cell membrane lysis and chemotaxis (the Office action states that Binder teaches the preceding with respect to black widow spider envenomations, but the subject matter cited from Binder pertains to *L. reclusus* envenomations).

The Office Action states that one of ordinary skill in the art would reasonably have expected the compounds described in Tomai and Gerster to be effective for treating dermal lesions caused by venom-induced dysregulation because (a) the compounds described in Tomai are known to be useful for treating T_H2-mediated disease, IgE-mediated diseases, and eosinophilia, and (b) blocking polymorphonuclear leukocyte activity, for example, with dapsone, is effective for treating spider envenomations.

Applicant respectfully disagrees with the position set forth in the Office Action. First, Applicant disagrees with the characterization of the teachings of Merigian and Blaho and Bitterman-Deutsch *et al.* stated in the Office Action as those teachings related to the present invention. Second, Applicant disagrees with the position of the Office Action equating the treatment of T_H2-mediated disease - as taught by Tomai - with treatment of T_H2-independent conditions such as those treatable using the methods of the present invention.

In responding to Applicant's previous arguments, the Office Action states, "Merigian and Blaho clearly teaches the infiltration of PMN (eosinophils and neutrophils) *in the necrotic inflammatory process*" (emphasis added). The Office Action seems to interpret this passage as teaching that eosinophils and neutrophils are *involved* in the inflammatory process associated with dermonecrosis so that inhibition of eosinophils would be effective to inhibit dermonecrosis. The reference actually teaches that histological examination of a necrotic spider bite area shows, among other things, "inflammatory infiltration with neutrophils and eosinophils." It does not follow that both subpopulations of PMN leukocytes (eosinophils and neutrophils) are involved in any necrotic process, inflammatory or otherwise.

Applicant's invention is drawn to treatment of lesions and dermonecrosis that result from T_H2-independent venom-induce immune dysregulation. The mere presence of eosinophils in a histological examination of a bite area provides no information regarding whether the eosinophils are, for example, activated, involved in a necrotic process, are present as a result of necrosis (e.g., chemotaxis after necrosis has occurred), are coincidentally present (e.g., co-localization of a T_H2-mediated condition at the site of dermonecrosis), etc. Conversely and significantly, the prior art does contain ample teaching as to (a) the presence and *affirmative role* of neutrophils in dermonecrosis, and (b) the active role of eosinophils in T_H2-*mediated* disease - conditions that are outside the scope of conditions treated by the methods of the present invention. Therefore, Applicant asserts that Merigian and Blaho does not teach infiltration of eosinophils and neutrophils *in the necrotic inflammatory process*, as stated in the Office Action. Merigian and Blaho merely teaches that histological examination of the bite area reveals the presence of eosinophils as well as neutrophils. There is no teaching or suggestion in Merigian and Blaho - or any other art - that eosinophils participate in any necrotic process. Applicant respectfully requests that if such art does, in fact, exist, that Applicant is given the chance to review such art. If eosinophils do not participate in any necrotic process, it is unclear why one of skill in the art would have been motivated to treat T_H2-independent lesions or prevent T_H2-independent dermonecrosis resulting from venom-induced immune dysregulation by inhibiting eosinophil activity.

Also in responding to Applicant's previous arguments, the Office Action states that Bitterman-Deutsch *et al.* discloses that one can treat necrotic cutaneous ulcers by blocking the activity of, generically, PMN. Applicant respectfully disagrees with this interpretation of Bitterman-Deutsch *et al.* The cited passage is an imprecise statement of the scope of dapsone activity. Dapsone interferes with neutrophil infiltration and suppress neutrophil adherence (see *Clinical Toxicology Review*, vol. 21, No. 9 (June 1999)). Furthermore, *whatever* anti-inflammatory effects dapsone provides seem to be related to the presence of neutrophils in the affected tissue. Bitterman-Deutsch *et al.* provides no teaching or suggestion that dapsone blocks activity of any subpopulation of PMN leukocytes other than neutrophils. Consequently, there is no teaching or suggestion in the cited references - or any other art - that dapsone has an inhibitory effect on eosinophils. Thus, it is unclear why one of ordinary skill in the art would have been motivated to substitute a compound known to inhibit eosinophils (e.g., an imidazoquinoline

amine or thizoloquinoline compounds) in a treatment for a condition treatable with a compound known to inhibit neutrophils (dapsone).

Even if, for the sake of argument, such motivation existed, one of skill in the art would not have had a reasonable expectation that the substitution of an eosinophil-inhibiting compound for the neutrophil-inhibiting compound would provide successful treatment for a neutrophil-mediated condition.

The rejection of independent claims 1 and 14 under 35 U.S.C. § 103(a) as being unpatentable over Tomai and Gerster in view of Bitterman-Deutsch *et al.*, Merigian and Blaho; Mosbech *et al.*, Binder, and Auerbach *et al.* is improper and should be withdrawn.

Claims 2-10 depend, directly or indirectly, from claim 1 and are allowable for at least all of the reasons set forth above regarding the allowability of claim 1. Claims 15-23 depend, directly or indirectly, from claim 14 and are allowable for at least all of the reasons set forth above regarding the allowability of claim 14.

In summary, the rejection of claims 1-10 and 14-23 under 35 U.S.C. § 103(a) as being unpatentable over Tomai and Gerster in view of Bitterman-Deutsch *et al.*, Merigian and Blaho; Mosbech *et al.*, Binder, and Auerbach *et al.* has been overcome. Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the above, Applicant submits that the application is in condition for allowance. Reconsideration of the application is requested.

Allowance of claims 1-10 and 14-23 at an early date is solicited.

Respectfully submitted,

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